Convergence and accommodation development is pre-programmed in premature infants

Article

Accepted Version

Horwood, A. M., Toor, S. and Riddell, P. M. (2015) Convergence and accommodation development is pre-programmed in premature infants. Investigative Ophthalmology & Visual Science, 56. pp. 5370-5380. ISSN 0146-0404 doi: https://doi.org/10.1167/iovs.14-15358 Available at https://centaur.reading.ac.uk/40636/

To link to this article DOI: http://dx.doi.org/10.1167/iovs.14-15358

Publisher: Association for Research in Vision and Ophthalmology

Convergence and accommodation development is pre-programmed in premature infants

Anna M Horwood[1,2] PhD

Sonia Toor[1] PhD

Patricia M Riddell[1] DPhil

University of Reading, UK

1. Infant Vision Laboratory, School of Psychology & Clinical Language Sciences, University of Reading, UK
2. Orthoptic Department, Royal Berkshire Hospital, Reading, UK

Word Count manuscript 5232 (excl title, abstract, refs, figs & tables)

Key Words Convergence Accommodation Development Prematurity Strabismus

Address for correspondence & reprints:-
Dr Anna Horwood, PhD, DBO(T)
School of Psychology & Clinical Language Sciences
University of Reading
Earley Gate
Reading
RG6 6AL
UK
a.m.horwood@reading.ac.uk Tel. (+44) 118 378 5553 Fax (+44) 118 378 6715

AH and ST were supported by a UK Medical Research Council Clinician Scientist Award G0802809 to AH

Abstract

Purpose This study investigated whether vergence and accommodation development in pre-term infants is pre-programmed or is driven by experience.

Methods 32 healthy infants, born at mean 34 weeks gestation (range 31.2-36 weeks) were compared with 45 healthy full-term infants (mean 40.0 weeks) over a 6 month period, starting at 4-6 weeks post-natally. Simultaneous accommodation and convergence to a detailed target were measured using a Plusoptix PowerRefII infra-red photorefractor as a target moved between 0.33m and 2m. Stimulus/response gains and responses at 0.33m and 2m were compared by both corrected (gestational) age and chronological (post-natal) age.

Results When compared by their corrected age, pre-term and full-term infants showed few significant differences in vergence and accommodation responses after 6-7 weeks of age. However, when compared by chronological age, pre-term infants' responses were more variable, with significantly reduced vergence gains, reduced vergence response at 0.33m, reduced accommodation gain, and increased accommodation at 2m, compared to full-term infants between 8-13 weeks after birth.

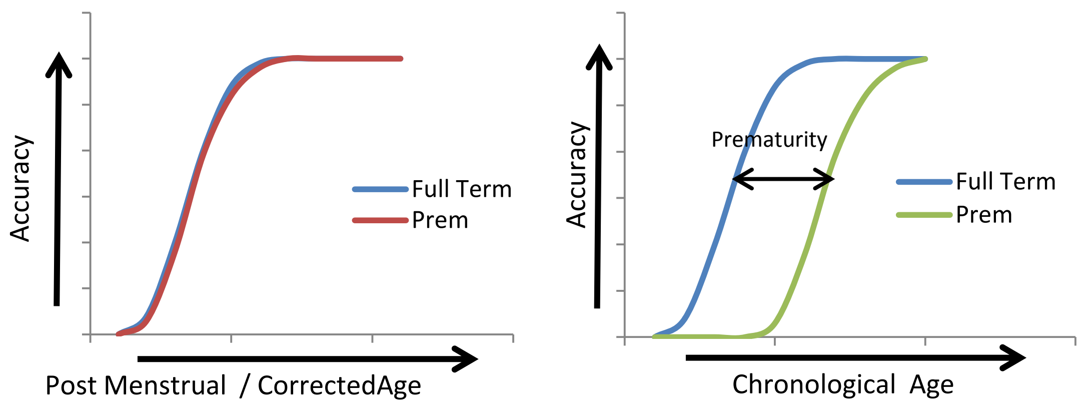
Conclusions When matched by corrected age, vergence and accommodation in pre-term infants show few differences from full-term infants' responses. Maturation appears pre-programmed and is not advanced by visual experience. Longer periods of immature visual responses might leave pre-term infants more at risk of development of oculomotor deficits such as strabismus.

Introduction

Bifoveal fixation is maintained by the precise coordination of vergence, versions and accommodation to maintain ocular alignment and image clarity. During post natal development, sensory fusion, motor fusion and accommodation become more closely coordinated[1-5] as visual experience acts on a basic genetic structure. It is unclear, however, whether these systems and relationships are initially pre-programmed and dependent on physical maturation, or influenced by visual experience from the outset. Comparing performance between pre-term and full-term infants provides an opportunity to explore these developmental processes. Figure 1 illustrates the two alternative possibilities[6]. If responses are mainly pre-programmed then both full-term and pre-term infants will reach maturity at the same corrected (post-conceptual / gestational) age but the pre-term infants will be older when compared by chronological (post-natal) age. If responses are more experience-dependent then both groups will reach maturity at similar chronological ages, but the pre-term infants will have reached this at an earlier stage of physical maturation (younger corrected age). Using this paradigm, previous research suggests that most sensory visual development is mainly pre-programmed and the earlier visual experience resulting from prematurity does not advance most aspects of visual development (for reviews see [7, 8]). The effect of prematurity on development of convergence and accommodation during early infancy, has only been described in studies of very small groups, but these also suggest a maturational time course for convergence [9] and accommodation [10] .

Importantly for this paper, however, a recent study by Jandó et al [6], found that the development of the binocular response to dynamic random dot correlograms (DRDCs) in pre-term infants depended on visual experience, not physical maturation. DRDCs are binocular stimuli that only elicit a characteristic visual evoked potential (VEP) in mature binocular systems[11] and are

Pre-Programmed/Maturational



Experience Dependent

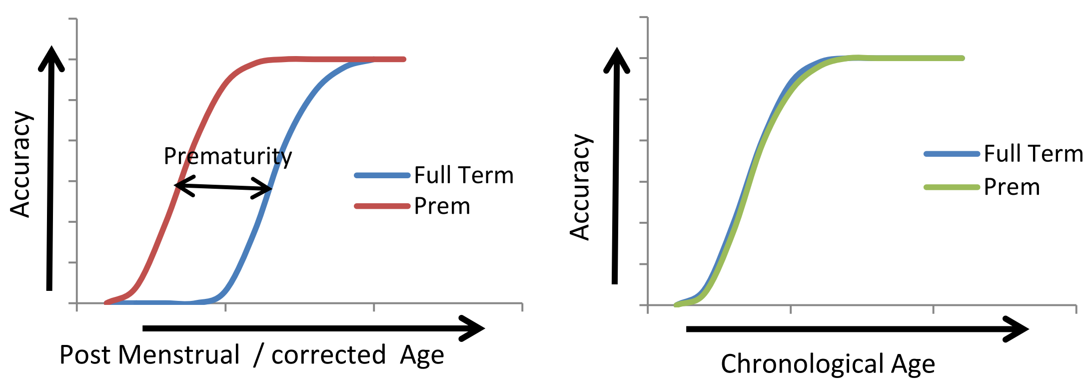


Figure 1. Illustration of differences in hypothetical development of mature responses (vergence and accommodation in this case) between full-term and pre-term infants in pre-programmed and experience-dependent scenarios (based on the illustration in Jandó et al[6] – with publisher's permission). The maturational hypothesis predicts that full- and pre-term infants' responses should develop at the same rate when matched by the corrected age (top left), but pre-term infants will be chronologically older when they mature (top right). The experience dependent hypothesis predicts that pre-term infants should develop mature responses before full-term infants when matched by the corrected age (lower left), but at the same chronological age (lower right).

therefore a marker for cortical binocularity in developing infants[12, 13]. The same study, however, found that pattern reversal VEP latency, which is a measure of integrity of the visual pathway, was not advanced by premature birth, so demonstrating that despite an immature visual pathway, the visual cortex can accept environmental stimulation from birth. These results provided a rationale for more detailed exploration of whether the development of convergence and accommodation is maturational or experiential: but there is also clinical relevance.

Children born pre-term are known to have a higher prevalence of accommodative [14], [15] and non-accommodative [16-18] strabismus. However, what causes this increased prevalence is unclear [19, 20]. We know that full-term neonates can have periods of ocular misalignment[21], inaccurate vergence and accommodation[1, 3] and even clinically diagnosed eye muscle palsies[22] without any apparent long term harm, but if misalignment persists or increases into the critical period for binocularity, the risk of strabismus, suppression and amblyopia is known to be severe. Tychsen has suggested that decorrelated sensory input between the eyes in the critical period for binocular vision is “a sufficient cause for infantile esotropia”[23].

We hypothesized that a mismatch in developmental timing between the sensory and motor components of binocularity could increase the risk of strabismus. If vergence development relates to the corrected age, it would develop later post-delivery in pre-term infants and so these infants would have longer with imprecise vergence and frequent misalignments. If experience-dependent sensory binocularity[6], which normally only emerges once vergence is more stable, emerges relatively earlier, immature vergence, which is normally of little consequence, would become a sufficient cause of decorrelated sensory input and be an additional risk factor for the development of strabismus.

This paper describes the development of vergence and accommodation in groups of low-risk pre-term and full-term infants in order to test the experience-dependent vs. maturational hypotheses.

Methods

The study adhered to the tenets of the Declaration of Helsinki and was approved and scrutinised by institutional and UK National Health Service Ethics Committees. Informed consent was obtained from the parents of all infants.

Participants

We defined the corrected age and the chronological age as recommended by the American Academy of Pediatrics Committee on Fetus and Newborn[24]. The chronological age was defined as the time elapsed from birth, while the corrected age was the chronological age reduced by the number of weeks born before 40 weeks of gestation. The corrected age was calculated from the expected delivery date calculated from the first day of the last menstrual period. 36 pre-term infants born between 31 weeks + 2 days and 36 weeks of gestational age (mean 34.09, SD 1.35weeks) were recruited from a local maternity hospital. Of these, 32 infants were able to be tested at least once. We chose not to study more premature infants where high rates of retinopathy of prematurity, general health complications, later developmental and perceptual difficulties [25] might have confounded the data. Three infants were also defined as "small for dates" (low birth weight for their gestational age) and two weighed less than 1500g (1465g and 1361g). None had suffered any perinatal or post-natal neurological complications, all were healthy when tested and none has subsequently developed strabismus and at the time of writing all are at least 2.5yrs old (corrected age).

Reasons for pre-term delivery were mainly twin pregnancy (53%) and pre-eclampsia (15%). We were unable to analyse the twin data separately. Of the many twins, we only collected data from both twins in six pairs, and rarely from both twins at the same visit. Only one set of monozygotic twins were tested.

Pre-term infants were compared with 45 typically developing full-term infants (born between at gestational age 37wks+2days – 42wks+1day: mean 40.0 weeks ±1.6 days), recruited from our departmental Infant Database. Data from these infants contributed to a previous publication, which reported data for the infants on visits when they showed no or minimal (less than +2.0D) hyperopia[3]. This paper reports some additional from 44 testing sessions in 19 infants (out of a total of 300 sessions) when these infants showed mild hyperopia (up to +3.0D at 16 weeks of age).

All infants were recruited soon after birth. We booked the first test at between 6 weeks corrected age for both groups (because younger infants are rarely testable[3]), although three younger infants were tested in the full-term group, then every two weeks until 20 weeks of age, and finally at 26 weeks of age. Since most aspects of binocular vision develop between 6 and 16 weeks [3, 4, 8, 12, 26, 27] we were not expecting that attempting to collect earlier data would help answer our research question.

Laboratory testing

A brief history was taken to confirm normal development and an orthoptic assessment excluded strabismus.

All infants were tested with a remote haploscopic photorefractor described previously[3, 28] (see Supplementary file). It incorporates a Plusoptix SO4 photorefractor in PowerRefII mode, which continuously and simultaneously records refraction and eye position at 25Hz, which allows us to calculate accommodation in diopters (D) and vergence in meter angles (MA). The photorefractor is set in a target presentation apparatus consisting of two concave mirrors and a moving monitor. The target appears to move backwards and forwards in front of the observer between distances of 0.25m and 2m (presented in a pseudo-random order of 0.33m (3D and 3MA demand), 2m (0.5D and MA), 0.25m (4D and MA), 1m (1D and MA), 0.5m (2D and MA). Meter angles are a preferable measure of vergence as they are a constant measure of response in relation to demand in populations where IPD varies between participants, and over the course of development. Thus for example, our 0.5m target presented to an infant with an IPD of 45mm would demand 2MA, 13.5 prism diopters or 7.68 degrees of convergence, while for an adult with an IPD of 60mm the same target would still demand 2MA, but 18 prism diopters or 10.2 degrees of convergence. MAs also provide an easy comparison between the appropriateness of vergence and accommodation for target demand at each distance. Data from the 0.25m target were not analysed for three reasons. Most commonly and importantly we find an unacceptable loss of data resulting from small pupils at this distance. There is also a small astigmatic error due to the mirror offsets (of subjectively approximately 0.5D at 25cm) but which reduces below 0.25D and is therefore not problematic at the other distances. Thirdly, the fusional stimulus is slightly different at 25cm because the far edges of the target screen fall slightly beyond the binocular fusional overlap of the lower mirror which is seen in physiological diplopia. We retain the target in the testing order so that a farther target always precedes a nearer one and vice versa.

Vergence and accommodation responses were measured while the infant watched a binocular, cartoon clown target containing a range of spatial frequencies as it moved backwards and forwards. Some target details were only separated by one pixel (visual angle of approximately 1 min arc at 0.33m) but it also contained large elements, high contrast edges, bright colours, alternating elements, eyes and a hairline to be maximally interesting to neonates with poorer visual acuity. The target subtended 3.15° at 2m and 18.3° at 0.33m. If possible each child was tested twice in each session and the data were averaged. The Plusoptix monitor allowed the tester to watch the infant in real time to assess attention and fixation and also to follow recording traces even when the accommodation responses exceeded the operating range of the photorefractor. We only report data collected when the infant was observed to have fixated the target steadily for at least 2 seconds at each fixation distance. The Plusoptix SO4 has a linear operating range of -7.0/+5.0D (i.e. up to 7D of accommodation and 5D of hyperopia). Beyond this, our unpublished calibrations and those of others [29] demonstrate that although the photorefractor continues to calculate a figure for refraction, this is an underestimation of the true value. This varies between individuals, so without individual calibration is not precisely quantifiable. Data from infants who demonstrated hyperopic refractive error over +5.0D estimated using maximum hyperopic refraction found during testing (MHR) were excluded before quantitative analysis. We have reported that MHR correlates closely with cycloplegic refraction in other child and infant groups[30].

Raw data were processed offline[3, 28]. Vergence in MA was calculated from the horizontal eye position of each eye, correcting for individually calculated angle lambda and inter-pupillary distance. Individual refraction calibrations and repeatability calculations were not possible for such young infants, but for group comparison studies such as this, averaged data is acceptable [29]. We calculated accommodation in diopters, using the increasingly myopic photorefraction which occurs on accommodation, with a correction for a slight systematic error (the photorefractor underestimates accommodative response by approximately 0.5D) using a formula derived from group calibration studies[28] using young adults. Calculations of response gain in relation to target demand (the slope of the stimulus response functions) used at least three data points (four if possible) at the different fixation distances. Where we report responses to particular targets, we have limited them to the nearest (0.33m, 3 MA & D) and the furthest (2 m, 0.5 MA & D).

Statistical Analysis and Data Presentation

We present our results in two ways. Firstly we provide descriptive figures to indicate the spread of responses. Since accommodation responses beyond the linear operating range of the photorefractor are likely to underestimate the degree of refraction to an unknown extent, this full dataset was not analysed statistically. If we had excluded these data completely, however, we felt we would have misrepresented the spread of infant behaviour.

We then calculated group means and 95% confidence intervals (CI) of all data within range. These data were analysed using two-way between-groups ANOVA (with age group and pre-term/full-term as factors), to investigate between-group differences in vergence and accommodation responses and gains at intervals of two weeks. A main effect of age indicates that vergence and/or accommodation change with age and a main effect of group indicates overall differences between pre-term and full-term infants. Most importantly, any age x group interaction would suggest that the two groups differ only at certain ages. If more between-group differences in responses are found when groups are compared by their corrected age, this would indicate that development of vergence and/or accommodation is experience-dependent. More group differences when groups are compared by their chronological age would suggest development is more maturational.

Post hoc testing used Bonferroni correction for multiple comparisons where appropriate.

<u>**Results**</u>

<u>*Testability and Repeatability*</u>

Numbers testable at each age point for both the corrected age and chronological age are illustrated in Table 1. While most infants provided usable data on most visits, only 4 pre-term and 13 full-term infants provided such data at every visit, so data were treated as crosssectional. Of the maximum potential number of testing sessions over the study period, 55% of the pre-term infants and 18% of in the full-term infants either were unable to attend or were not able to be tested at all due to being asleep or fretful on a booked session. Premature infants, particularly the large number of twins, were especially difficult to test regularly. These factors added to the normal difficulties of testing infants. But if an infant attended and was attentive, complete runs of targets at the different fixation distances were always recorded. Repeated measurements within a single visit were more often possible for older infants, whether full term or pre-term (e.g.23% repeatable at 6-7 weeks and 58% at 12-13 weeks of corrected age for the pre-term infants). Repeated measurements were averaged where available. Variability in repeated measurements *within* individuals was similar to that *between* different infants at each corrected age point (95% confident intervals were not significantly different), but younger infants were much more variable overall (95%CI for vergence gain at 6-7 weeks: between individuals = ±0.12; within an individual = ±0.09; while at 12-13 weeks: between individuals = ±0.045; within an individual = ±0.04).

Exclusions and Refraction

Myopia did not exceed -0.5D for any infant tested. Some of the youngest infants behaved myopically (over accommodated) for distance fixation. However, their accommodation relaxed at least once during testing to an emmetropic or hyperopic refraction, confirming that they were not genuinely myopic.

One pre-term infant appeared consistently significantly more than 5.0D hyperopic on multiple visits and their data were excluded completely from further analysis. 2 (6.2%) premature infants, and 4 (8.8%) full-term infants showed >5.0D hyperopia (beyond the linear operating range of the photorefractor) fleetingly (i.e. for a single data point) at some time, all in the first 12 weeks of life and the data from that single session were excluded (Table 1). No refraction from these

Age at testing	4-5 wks	6-7 wks	8-9 wks	10-11 wks	12-13 wks	14-15 wks	16-17 wks	18-19 wks		24-27 wks
FULL-TERM										
Total tested (of 45 in study)	**1***	**31**	**36**	**37**	**33**	**31**	**29**	**31**		**36**
Hyperopic session excluded		2	3	1	0	0	0	0		0
Unrecordable e.g. pupils/lids, point excluded	0	2	2	1	0	0	0	1		0
Accom out of range (>7D) point excluded	0	3	6	2	0	0	0	0		0
% datapoints excluded	0%	4.0%	5.5%	2.0%	0%	0%	0%	0.6%		0%
PRE-TERM (of 32 in study)										
Corrected Age Total tested	**16**	**24**	**22**	**19**	**22**	**16**	**4**	**7**		**24**
Hyperopic session excluded	1	1	0	1	1	0	0	0		0
Unrecordable e.g. pupils/lids point excluded	0	0	1	0	1	2	0	0		0
Accom out of range (>7D) point excluded	5	5	3	1	2	0	0	0		0
% datapoints excluded	7.8%	5.2%	4.5%	1.3%	3.4%	3.1%	0%	0%		0%
Chronological Age Total tested			**3**	**17**	**24**	**16**	**23**	**16**		**27**
Hyperopic session excluded			1	0	1	0	0	0		0
Unrecordable e.g. pupils/lids point excluded			1	0	0	1	1	1		0
Accom out of range (>7D) point excluded			0	6	6	3	1	0		0
% datapoints excluded			8.3%	8.8%	6.2%	6.2%	2.1%	1.5%		0%

Table 1. Numbers testable at each age point. Pre-term infants were delivered on average six weeks early. At 8-9 weeks chronological age a pre-term infant would be equivalent developmentally to a 2-3 week full-term infant and therefore less likely to supply usable data.

* *only three infants were enrolled in the study at this age, but for all other participants the first scheduled appointment was at 6 weeks*

infants ever exceeded a photorefractor calculation of +7.0D hyperopia. No infant whose session data were excluded showed evidence of manifest refraction >+3.00D by 16 weeks of age, so all had emmetropized to within normal limits

The proportion of infants with hyperopia greater than +2.0D in each group were similar across time when compared by their corrected age e.g. 39% vs 33% respectively at 10-11 weeks and 29% vs 25% at 14-15 weeks. At 24-27 weeks of corrected age the infants' mean refraction estimated by the MHR measured during the testing session was +0.18D (95%CI -0.25D / +0.66D) in the full-term infants and +0.28D (95%CI -0.43 / +0.99D) in the pre-term infants ($t(55)=1.36$, $p=0.178$, n.s.).

Full Dataset

Figure 2 illustrates the ranges of vergence and accommodation responses at two time points, 6-7 weeks of corrected age (which was on average 12-13 weeks of chronological age for the pre-term group), and again at 12-13 weeks of corrected age (18-19 weeks of chronological age for the pre-term infants). We chose these two time points as 6-7 weeks is before mature binocular responses develop in full-term infants, while 12-13 weeks is when vergence and accommodation are not significantly different from adults[3], and sensory binocularity is typically emerging[4].

Figure 2 illustrates the whole dataset including out-of-range accommodation estimates (gray shaded areas). 42 individual datapoints (2.3% of the total tested) exceeded the linear operating range of the phororefractor (>7D accommodation). 24 infants (evenly distributed between pre-term and full-term) provided these datapoints fleetingly for the nearest targets in their first 12 weeks (corrected age if pre-term) and for all except one infant in each group these were between approximately 7.0D and 10.0D. The other two infants contributed six datapoints between approximately 10.0D and 12.0D).

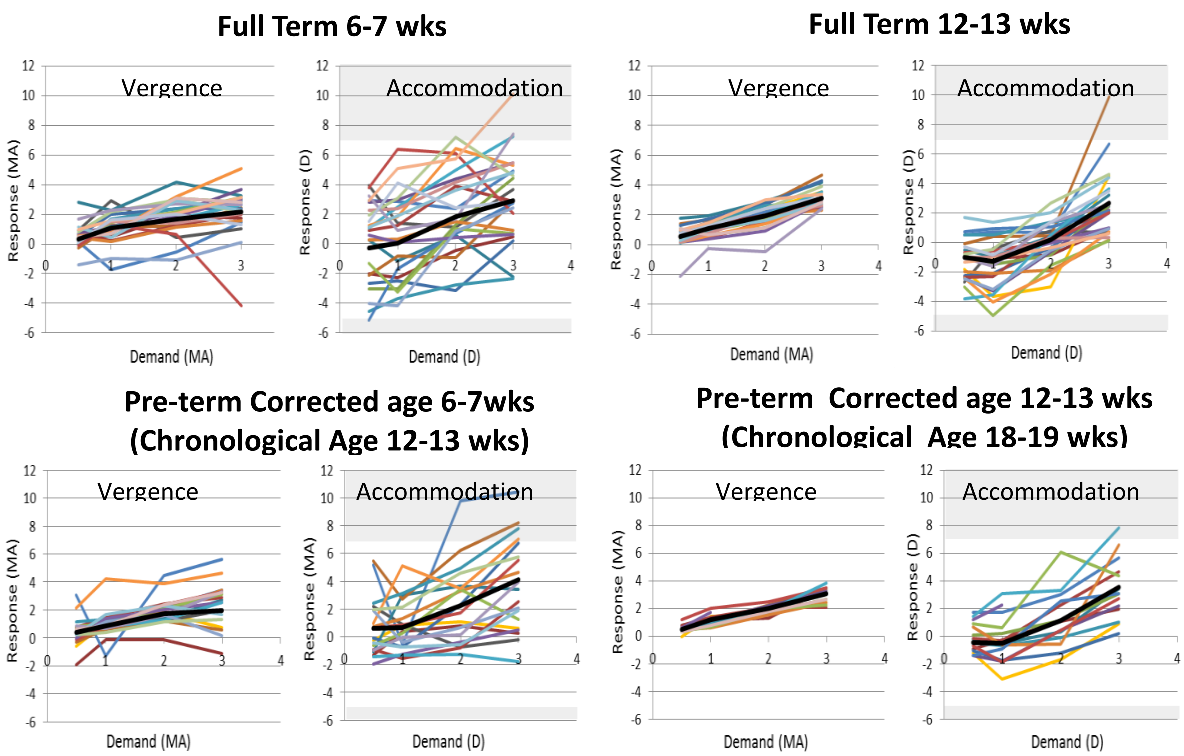


Figure 2 . Recorded responses (y-axis) in relation to demand (x-axis), including out-of-linear-range accommodation estimates (gray shaded areas). Black line = mean response.
Left: Full-term infants at 6-7 weeks of age (top), and pre-term infants of 12-13 weeks of chronological age (bottom), but equivalent corrected age.
Right: Full-term infants at 12-13 weeks of age (top), and pre-term infants of 18-19 weeks of age (bottom).

There are two important comparisons in Figure 2. The first is a corrected age match comparison (full-term (top charts) vs pre-term infants (bottom charts)), where performances are similar. Many of the youngest full-term and corrected age pre-term infants (left charts in figure) showed highly erratic accommodation. What we have previously termed "all or nothing" patterns [3] were common, where accommodation response to an approaching target was flat for the more distant targets, but then was either appropriate or excessive (and sometimes out-of-range) for the nearest target, despite concurrent linear vergence. 11 (6.9%) of the 198 individual data points collected at 0.33m in the pre-term infants, and 19 (6.5%) of the 291 points collected in the full-term infants were greater than 7.0D. Before 12 weeks of age, over-accommodation for the nearest target exceeded 4.5D at 0.33m in 28.5% of full-term infants and 38.5% of the corrected age pre-term infants.

The second comparison is between full-term infants with pre-term infants matched by chronological age. It was not possible to compare full term with pre-term infants at 6-7 weeks since insufficient data was collected from the pre-term infants, but the comparison at 12-13 weeks is illustrated in the top right and bottom left of the figure. This shows that full-term infants' vergence and accommodation is more linear than chronologically age-matched pre-term infants.

Analysis of Data in Range

For statistical analysis we compared infants matched by both their corrected age and chronological age, considering response gain as well as responses for near (0.33m) and distance (2m). Vergence measurements were all within the linear range of the photorefractor across the range tested, so all infants' vergence gains were calculated using responses at 4 distances. For accommodation, out-of-range points were excluded and gains were calculated from the responses to the three remaining distances. Gains thus calculated are likely to be a slight underestimate of the true gain. Such exclusions occurred most frequently at 8-9 weeks corrected age. Here the median accommodation response for the 0.33m target of the full data set (using out-of-range point which we know are inaccurate) was 0.34D more than the mean of the more selected data. If the median from the full dataset had been used to calculate the gain, it would have increased the gain by 0.12. At other ages differences were less. Four accommodation data points were available for 93% of the target runs for the full-term infants and 90% of those from the pre-term infants.

		Corrected Age			Chronological Age		
		F	p	η^2	F	p	η^2
Vergence Gain	Age in weeks	11.68	**.000**	**.207**	**20.625**	**.000**	**.044**
	Prem /Term	1.32	.251	.003	**5.299**	**.000**	**.106**
	Age x Prem/Term interaction	4.46	**.000**	**.091**	**4.819**	**.000**	**.079**
Vergence at 2m	Age in weeks	**3.36**	**.000**	**.070**	**3.919**	**.048**	**.009**
	Prem /Term	0.01	.934	.000	**3.053**	**.001**	**.064**
	Age x Prem/Term interaction	1.02	.428	.022	**2.108**	**.034**	**.036**
Vergence at 0.33m	Age in weeks	**14.31**	**.000**	**.249**	**12.785**	**.000**	**.029**
	Prem /Term	0.39	.533	.001	**7.383**	**.000**	**.145**
	Age x Prem/Term interaction	**4.18**	**.000**	**.088**	**5.733**	**.000**	**.096**
Accom Gain	Age in weeks	**2.31**	**.012**	**.049**	.039	.843	.000
	Prem /Term	2.29	.131	.005	**2.397**	**.009**	**.051**
	Age x Prem/Term interaction	**2.73**	**.003**	**.057**	**3.819**	**.000**	**.064**
Accom at 2m	Age in weeks	**2.33**	**.011**	**.050**	**11.885**	**.001**	**.026**
	Prem /Term	**14.94**	**.000**	**.033**	1.135	.334	.025
	Age x Prem/Term interaction	**1.98**	**.033**	**.043**	**3.933**	**.000**	**.066**
Accom at 0.33m	Age in weeks	**1.97**	**.035**	**.045**	**11.583**	**.001**	**.027**
	Prem /Term	**29.46**	**.000**	**.065**	**3.105**	**.001**	**.068**
	Age x Prem/Term interaction	1.67	.086	.038	1.429	.182	.026

Table 2 Results of ANOVA of vergence and accommodation gains and responses at 2m and 0.33m. Significant differences are shaded.

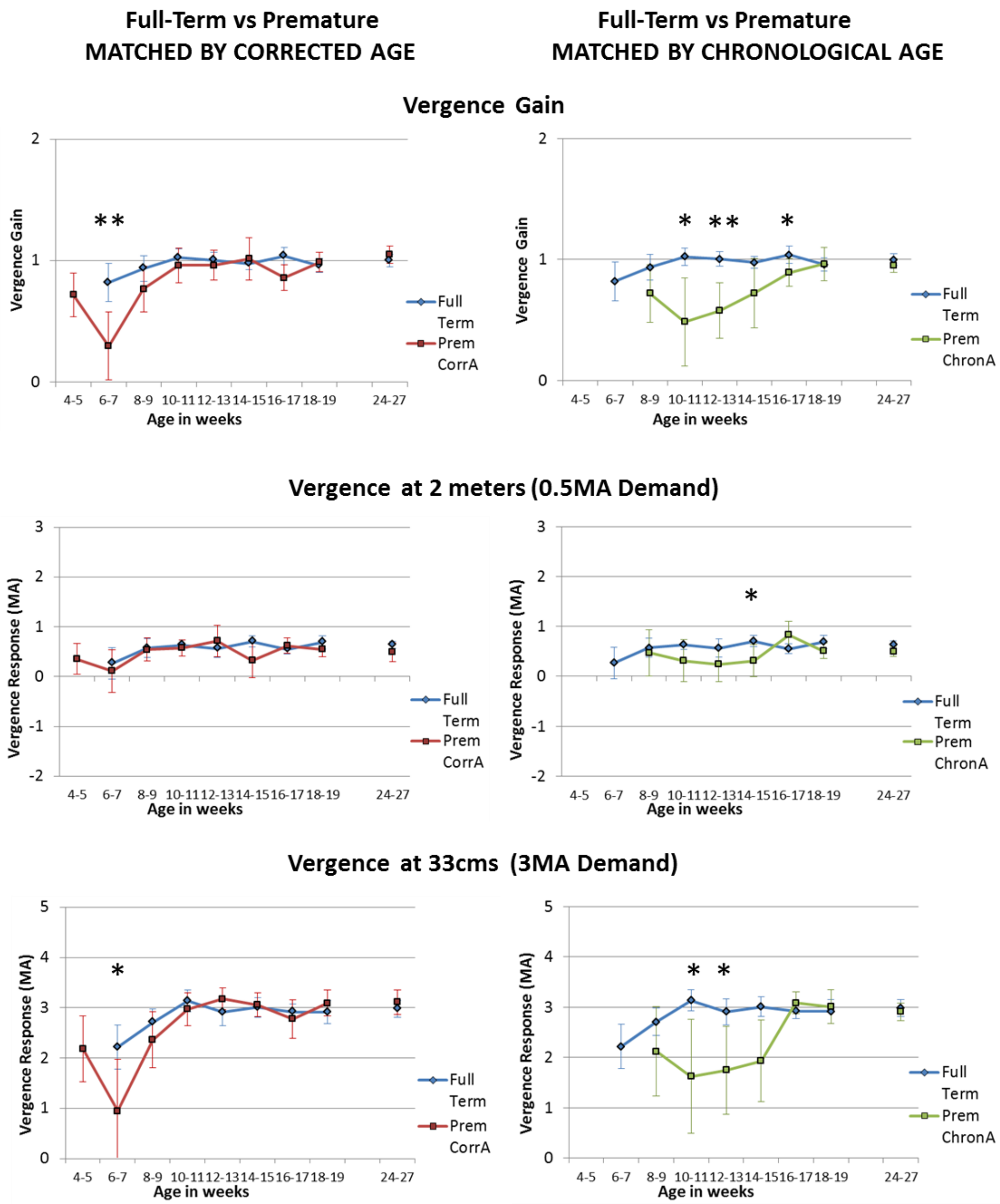


*Figure 3 Vergence gain (top), vergence responses to target at 2 meters (center) and vergence responses to target at 0.33m (lower). Left column: responses matched by corrected age. Right column: responses matched by chronological age. Statistically significant differences on post-hoc testing indicated by asterisks. Error bars indicate 95% confidence intervals. * indicates p<0.05; **indicates p<0.01*

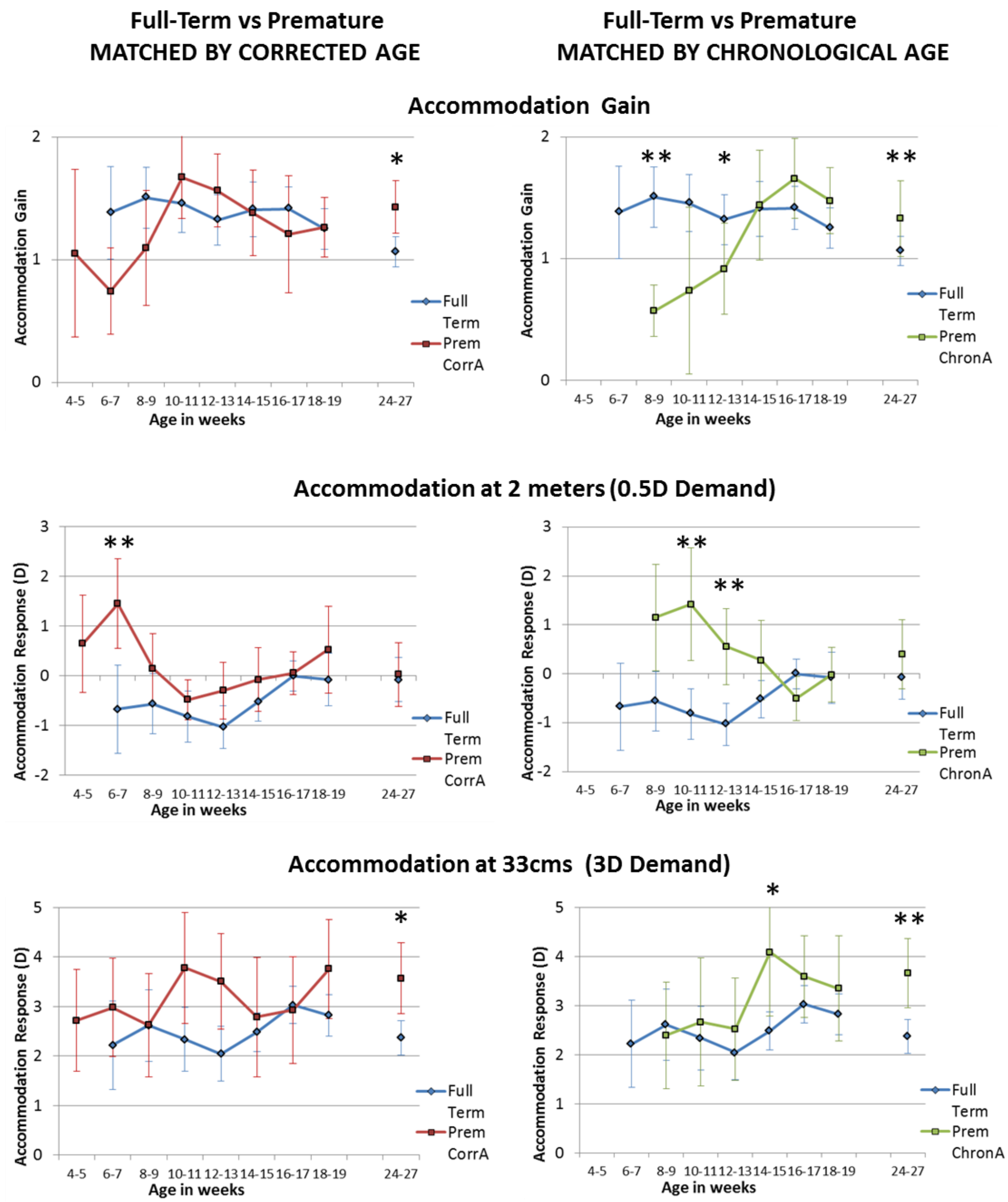


*Figure 4 Accommodation gain (top) calculated from at least three fixation distances, and actual responses at 2 meters (center) and 0.33m (lower). Left column: responses matched by corrected age. Right column: responses matched by chronological age. Statistically significant differences on post-hoc testing indicated by asterisks. Error bars indicate 95% confidence intervals. * indicates p<0.05; ** indicates p<0.01*

Results of the ANOVAs comparing response gains and responses at 2m and 0.33m between groups are shown in Table 2 and post hoc significant differences are indicated in Figures 3 (vergence) and 4 (accommodation).

Again, we compared groups matched by both corrected and chronological age. When matched by their corrected age there were the expected significant developmental improvements in all infants. Pre-term infants relaxed their accommodation significantly less at 2m than the full-term infants, but there were no other overall group differences. There were significant age x group interactions in four of the six comparisons but post-hoc testing showed that differences were only significant at 6-7 weeks of age (Figures 3 and 4), where the pre-term infants under-converged for near, and over-accommodated for distance targets. Subsequently, up to 24-27 weeks, there were no differences in accommodation and vergence responses between full-term and pre-term infants matched by their corrected age.

When infants were matched by chronological age there were significant pre-term/ full-term group differences for all comparisons except accommodation at 2m. Full-term infants showed more appropriate responses than the chronologically age matched pre-term infants (gain closer to 1, responses closer to the target demand). There was also a significant age x group interaction for all comparisons except accommodation at 0.33m. Post hoc testing showed that the majority of significant differences were found between infants aged between 10-16 weeks and were particularly clear at 10-11 weeks of age. While the full-term infants' responses appeared to have matured (were similar to responses at the oldest age tested), those of the pre-term infants were still immature.

To test the linearity of vergence and accommodative responses for each group we calculated correlation coefficients (r^2) for individual stimulus response slopes where four data points (at 0.33m, 0.5m, 1m and 2m) were available. Infants matched by their corrected age demonstrated similar linearity of response e.g. for vergence at 12-13 weeks mean r^2 were 0.94 and 0.91 respectively for full-term and the corrected age pre-term infants. However, when matched by chronological age 12-13 week pre-term infants demonstrated less linear vergence (r^2 = 0.77 for pre-term infants and 0.94 for full-term infants)(t=2.57,p=0.019)), not significantly different from full-term infants at 6-7 weeks. Similar analysis for accommodation showed that mean r^2 for the full-term and the corrected age pre-term infants did not differ significantly (0.74 and 0.77 respectively), but pre-term infants of the same chronological age had a lower mean r^2 of only 0.53 (t(39)=2.4,p=0.02), again not-significantly different from full-term infants at 6-7 weeks.

Discussion

This study investigated the developmental time course for vergence and accommodation responses in full-term and pre-term infants matched by both chronological and corrected age. Our results suggest that vergence and accommodation in pre-term infants follow a maturational developmental trajectory and that responses are not accelerated by the additional visual experience of earlier birth. Full-term infants show more adult-like vergence and accommodation responses when compared to chronologically age-matched pre-term infants.

These results contrast with those of Jandó et al[6] who showed an experience-dependent development of sensory binocularity, where the additional visual experience in preterm infants resulted in earlier development. 50% of Jandó et al's [6] pre-term infants responded to DRDCs by 1.92 months post-natally (approximately 8 weeks). If sensory binocularity develops earlier in pre-term infants, but accommodation and vergence responses do not, then early development of sensory binocularity is unlikely to be the cause of maturation of vergence and accommodation. Instead, it is possible that the oculomotor system supports or reinforces the development of sensory binocularity.

Vergence

Vergence accuracy and a gain close to one characterize adult-like responses. More recent research has demonstrated that, in full-term infants, vergence is adult-like by 8-9 weeks[1, 3], earlier than suggested by older literature where such young infants were not assessed [31] or good vergence responses less commonly found[4]. The early large neonatal misalignments found in infants younger than 2 months of age are also reducing dramatically [21 4, 31]. Thus good alignment for targets at all fixation distances is typically in place before the onset of stereopsis and sensory binocularity (Wong A et al. IOVS 2008;49:e-abstract 3748) [8 26, 32-34]. In contrast, our pre-term infants still showed immature vergence until about 15 weeks of age.

If sensory and oculomotor visual systems had been found to mature in parallel, then the effects of prematurity on visual development would be insignificant as the onset of critical periods for vergence control and sensory binocularity would be similarly delayed. However, if any aspect of sensory binocularity (with concurrent susceptibility to suppression and amblyopia) can be advanced by experience, while oculomotor control is not, a mismatch of developmental trajectories might result in decorrelated input from each eye to the visual cortex at a time when cortical binocularity is entering a critical period that has been advanced through early visual experience.

Additional infant studies have demonstrated that development of stereopsis does not depend on the development of vergence [35 4]. Thorn at al[4] suggest that good alignment is not necessary for *development* of the neural mechanisms underlying binocular vision, but is necessary for *maintenance* of these mechanisms. Tychsen argues that “binocular decorrelation is a sufficient cause of infantile esotropia when imposed during a critical period of visuomotor development”[23]. Immature biases to esodeviation such as asymmetrical monocular OKN[27] and better convergence than divergence[36] may be retained in premature infants, resulting in an increased risk of infantile esotropia. Our findings therefore suggest a mechanism that might account for increased prevalence of strabismus in pre-term infants.

Accommodation

Immature accommodation is more erratic and less linear than vergence at the same age. In pre-term infants, this variability is extended for longer after birth. Lower gain was often the result of over-accommodation in the distance, but excessive accommodation for near was also common, often after almost flat responses to the three farther targets, as has been found in previous studies[3, 37]. Accommodation development in pre-term infants also related to their corrected age rather than their chronological age, with the same gradual increase in accommodation gains over the first weeks that Banks found for two younger full-term infants using dynamic retinoscopy[10]. Banks' research also suggested a similar pre-programmed course of development. We did not detect, however, the same clear developmental trajectory of accommodation development in full-term infants as reported by Banks[10] because most of our full-term infants were already showing response gains of well over 1.0 (and which related to their refraction) by 6-7 weeks.

Our results suggest that not only are vergence inaccuracies occurring when cortical binocularity could be emerging, but the linkages between vergence and accommodation will be less consistent during this extended period of mismatched retinal input and imprecise accommodation. Although we have reported that *mean* full-term infant AC/A ratios are not significantly different from those of adults[5], the variability of response in preterm infants would result in a weaker linkage between vergence and accommodation responses for a greater developmental period. Thus, increased risk of strabismus in preterm infants might also be driven by lack of reinforcement of AC/A and CA/C ratio linkages.

Finally, good accommodation is also implicated in emmetropization [38, 39]. Previous studies have shown that binocular input dramatically enhances not only vergence but also accommodation in full-term infants[1, 3], older children and adults[28]. As well as inaccurate vergence (and so inter-ocular decorrelation) being a “sufficient” cause of esotropia, any damage to cortical binocularity might then also damage accommodation, and thus be implicated in the defective emmetropzation that is more common in those born both pre-term [40] and with strabismus[41] . Thus, prematurity may not only cause infantile esotropia, but might also be implicated in strabismus with an accommodative element.

Study Limitations

While comparisons of these data with those of Jandó et al[6] support our arguments above, there are differences in testing paradigm between the two studies which might explain apparent differences between developmental time courses between the groups for other reasons. Jandó et al [6] measured cortical activity which required no behavioural response. VEP is easier to test successfully in very young infants and VEP testing is a less demanding task than our paradigm. Our task involves a longer processing time, requires a motor response to a sensory signal, and is more likely to be susceptible to attentional variation. It is therefore possible that the attentional system in premature infants needs to have reached a sufficient level of maturity for them to perform the tests used here. In this case, the difference in timing between full term and preterm infants might be the result of differences in maturation of higher order behavioural mechanisms rather than maturation of vergence and accommodation per se.

All infants, especially pre-term twins, present a significant challenge in testing, so a complete set of longitudinal data was rare, and many testing sessions were abandoned or cancelled for reasons unrelated to the study. However, this is only likely to affect the quantity, not the quality of the results. Despite small numbers in the youngest infant groups, statistical significance was still reached.

We could not definitively differentiate attentional and physical immaturity, but either means that pre-term infants will have inaccurate vergence and accommodation for longer after birth. Immature responses could be due to immaturity of the control mechanisms, so despite sensory detection of the change of target distance, rapid, co-ordinated physical responses cannot yet occur. Alternatively, acuity, attention or interest in detailed targets may be insufficiently developed to drive appropriate responses. Accommodation is certainly active in very early infancy, as evidenced by the difference between cycloplegic (generally hyperopic) and non-cycloplegic (generally myopic) refraction of neonates (for review see Thorn et al [42]), and convergence is also clearly possible during frequent large neonatal misalignments[21], but seems poorly controlled. We also accept that the reduction in variability of responses from the older infants could also partly be due to averaging of more infants' data, but even the averaged data became less variable with time.

A major limitation of the Plusoptix photorefractor is its relatively small operating range. Although out-of-range accommodation responses were still collected, we could not measure them accurately because calculations from the Plusoptix become non-linear, so a reading of 8D might be the given from an accommodative response of between 7D and 9D, and this error may vary between individuals. By excluding these points our statistical testing used a slightly smaller dataset (and probably under-estimated mean over-accommodation), but the type and proportions of excluded data were similar in each group. We continue to use the Plusoptix photorefractor because it is one of the few instruments able to refract and assess eye position binocularly, naturalistically, simultaneously and continuously.

We considered excluding the very non-linear responses, where a pattern of flat or low gain responses was found to targets at 0.5m or beyond, with a sudden large over-accommodation response to the 0.33m target. These responses are different from largely linear adult responses and were sometimes out of the linear range of the photorefractor. By excluding them, however, we would miss-describe neonatal responses, of which they are a feature. We accept that when the excessive near response is out-of-linear-range they are difficult to quantify using our equipment, but they are of interest for two reasons. Flat accommodation responses for more distant targets, followed by appropriate or excessive accommodation for near suggest that while vergence seems generally well controlled over the linear range of target distances, accommodation can be driven independently once a level of blur (or disparity) reaches a threshold. These responses also have implications for the development of the AC/A ratio because they suggest that the relationship between accommodation and vergence is different at different target demands, suggesting that in infancy A/C linkages are unstable.

We could also not perform the individual calibrations for accommodation that would have been ideal for such studies[29], although group comparisons are often used in studies such as this. The Plusoptix photorefractor accuracy compares well with refraction derived from retinoscopy (around +/- 0.75D)[28, 43], while our measure of vergence change is more precise because we correct for variables such as IPD and angle lambda[28] . There may therefore have been some individual between-participant differences in accuracy of refraction within the operating range of the photorefractor, but there should be no optical reasons why calculation of refraction of younger or premature infants *per se* should be less accurate (once data is captured). The fact that more linear vergence was demonstrated simultaneously with erratic accommodation shows the infants were attending to the target and refraction was on-axis, but frequently well outside ranges which could be attributed to measurement error.

We had too few significantly hyperopic infants to investigate early hyperopia as a separate issue. We had similar proportions of apparently hyperopic infants in each of our groups when matched by their corrected age, so this is unlikely to have affected our results.

In conclusion, vergence and accommodation follow a pre-programmed developmental trajectory so pre-term infants appear to have longer visual experience of immature responses. This may extend into the period when experience-dependent cortical binocularity emerges. A mismatch in the time course between the development of oculomotor and sensory binocularity might contribute to the increased risk of strabismus in children born pre-term.

Acknowledgements

Financial conflicts of interest – none. AH and ST were supported by UK Medical Research Council Clinician Scientist Fellowship G0802809. We are very grateful for help and advice in planning and carrying out recruitment of the pre-term infants given by Dr Greg Boden, Consultant Paediatrician, and Research Nurses Sue Hallett and Morag Zelisko at the Royal Berkshire Hospital, Reading, UK

References

1. Bharadwaj S, Candy T. Cues for the control of ocular accommodation and vergence during postnatal human development. *Journal of Vision* 2008;8:1-16.
2. Bharadwaj SR, Candy TR. Accommodative and vergence responses to conflicting blur and disparity stimuli during development. *Journal of Vision* 2009;9:1-18.
3. Horwood A, Riddell P. Developmental changes in the balance of disparity, blur and looming/proximity cues to drive ocular alignment and focus. *Perception* 2013;42:693-715.
4. Thorn F, Gwiazda J, Cruz A, Bauer J, Held R. The development of eye alignment, convergence, and sensory binocularity in young infants. *Invest Ophthalmol Vis Sci* 1994;35:544-553.
5. Turner JE, Horwood AM, Houston SM, Riddell PM. Development of the response AC/A ratio over the first year of life. *Vision Res* 2002;42:2521-2532.
6. Jandó G, Miko-Barath E, Marko K, Hollody K, Torok B, Kovacs I. Early-onset binocularity in preterm infants reveals experience-dependent visual development in humans. *Proc Natl Acad Sci U S A* 2012;109:11049-11052.
7. Birch EE, O'Connor AR. Preterm birth and visual development. *Seminars in neonatology: SN* 2001;6:487-497.
8. Braddick O, Atkinson J. Development of human visual function. *Vision Res* 2011;51:1588-1609.
9. Weinacht S, Kind C, Monting JS, Gottlob I. Visual development in preterm and full-term infants: a prospective masked study. *Invest Ophthalmol Vis Sci* 1999;40:346-353.
10. Banks MS. The development of visual accommodation during early infancy. *Child Dev* 1980;51:646-666.
11. Markó K, Kiss HJM, Mikó-Baráth E, et al. Contrast independence of dynamic random dot correlogram evoked VEP amplitude. *Journal of Vision* 2009;9. 8.1-10. doi: 10.1167/9.4.8.

12. Birch E, Petrig B. FPL and VEP measures of fusion, stereopsis and stereoacuity in normal infants. *Vision Res* 1996;36:1321-1327.

13. Braddick O, Atkinson J, Julesz B, Kropfl W. Cortical binocularity in infants. *Nature* 1980;288:363-365.

14. Mohney BG, Lilley CC, Green-Simms AE, Diehl NN. The Long-term Follow-up of Accommodative Esotropia in a Population-based Cohort of Children. *Ophthalmology* 2011;118:581-585.

15. Coats DK, Avilla CW, Paysse EA, Sprunger DT, Steinkuller PG, Somaiya M. Early-onset refractive accommodative esotropia. *J AAPOS* 1998;2:275-278.

16. Maconachie GD, Gottlob I, McLean RJ. Risk factors and genetics in common comitant strabismus: a systematic review of the literature. *JAMA Ophthalmology* 2013;131:1179-1186.

17. Major A, Maples WC, Toomey S, DeRosier W, Gahn D. Variables associated with the incidence of infantile esotropia. *Optometry - Journal of the American Optometric Association* 2007;78:534-541.

18. Holmstrom G, el Azazi M, Kugelberg U. Ophthalmological follow up of preterm infants: a population based, prospective study of visual acuity and strabismus. *Br J Ophthalmol* 1999;83:143-150.

19. Pennefather PM, Clarke MP, Strong NP, Cottrell DG, Dutton J, Tin W. Risk factors for strabismus in children born before 32 weeks' gestation. *Br J Ophthalmol* 1999;83:514-518.

20. Pennefather PM, Tin W, Strong NP, Clarke MP, Dutton J, Cottrell DG. Refractive errors in children born before 32 weeks gestation. *Eye (Lond)* 1997;11 (Pt 5):736-743.

21. Horwood A. Maternal observations of ocular alignment in infants. *J Pediatric Ophthalmol & Strab* 1993;30:100-105.

22. Elston JS, Timms C. Clinical evidence for the onset of the sensitive period in infancy. *Br J Ophthalmol* 1992;76:327-328.

23. Tychsen L. Causing and curing infantile esotropia in primates:the role of decorrelated binocular input (an American Ophthalmological Society Thesis. *Trans Am Ophthalmol Soc* 2007;105:564-593.

24. Committee on Fetus and Newborn. Age Terminology During the Perinatal Period. *Pediatrics* 2004;114:1362-1364.

25. Dutton GN. The spectrum of cerebral visual impairment as a sequel to premature birth: an overview. *Doc Ophthalmol* 2013;127:69-78.

26. Braddick O, Atkinson J. The development of binocular function in infancy. *Acta Ophthalmol (Copenh)* 1982;27-35.

27. Wattam-Bell J. Motion processing asymmetries and stereopsis in infants. *Vision Research* 2003;43:1961-1968.

28. Horwood A, Riddell P. The use of cues to convergence and accommodation in naïve, uninstructed participants. *Vision Research* 2008;48:1613-1624.

29. Bharadwaj S, Sravani N, Little J-A, et al. Empirical variability in the calibration of slope-based eccentric photorefraction. *J Opt Soc Am A* 2013;30:923-931.

30. Horwood A, Riddell P. Receding and disparity cues aid relaxation of accommodation. *Optometry & Vision Science* 2009;86:1276-1286.

31. Bobier WR, Guinta A, Kurtz S, Howland HC. Prism induced accommodation in infants 3 to 6 months of age. *Vision Res* 2000;40:529-537.

32. Leguire LE, Rogers GL, Bremer DL. Visual-evoked response binocular summation in normal and strabismic infants. Defining the critical period. *Invest Ophthalmol Vis Sci* 1991;32:126-133.

33. Petrig B, Julesz B, Kropfl W, Baumgartner G, Anliker M. Development of stereopsis and cortical binocularity in human infants: electrophysiological evidence. *Science* 1981;213:1402-1405.

34. Wong A, Tychsen L, Foeller P, Burkhalter A. Effects of De-Correlated Binocular Input to the Developing Brain. *Invest Ophth Vis Sci* 2008;49:e-abstract 3748.

35. Birch E, Gwiazda J, Held R. The development of vergence does not account for the onset of stereopsis. *Perception* 1983;12:331-336.

36. Horwood A. Neonatal misalignments reflect vergence development but rarely become esotropia. *Brit J Ophthalmol* 2003;87:1146-1150.

37. Riddell P, Grose-Fifer J, Hainline L, Abramov I. Photorefractive evaluation of infant accommodation and convergence. *Topical mtg of the Optical Society of America, Non-invasive assessment of the visual system.* Santa Fe, NM; 1991.

38. Ingram RM, Gill LE, Goldacre MJ. Emmetropisation and accommodation in hypermetropic children before they show signs of squint--a preliminary analysis. *Bull Soc Belge Ophtalmol* 1994;253:41-56.

39. Mutti DO, Mitchell GL, Jones LA, et al. Accommodation, acuity, and their relationship to emmetropization in infants. *Optom Vis Sci* 2009;86:666-676.

40. Saunders K, McCulloch D, Shepherd A, Wilkinson A. Emmetropisation following preterm birth. *Br J Ophthalmol* 2002;86:1035-1040.

41. Ingram RM, Gill LE, Lambert TW. Emmetropisation in normal and strabismic children and the associated changes of anisometropia. *Strabismus* 2003;11:71-84.

42. Thorn F, Gwiazda J, Held R. Using near retinoscopy to refract infants. In: Vital-Durand F, Atkinson J, Braddick O (eds), *Infant Vision.* Oxford: Oxford University Press; 1996:113-124.

43. Mirzajani A, Heirani M, Jafarzadehpur E, Haghani H. A comparison of the Plusoptix S08 photorefractor to retinoscopy and cycloretinoscopy. *Clin Exp Optom* 2013;96:394-399.